

TITLE: Can pregabalin reduce the frequency and severity of dry eye symptoms after laser-assisted in situ keratomileusis?

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Protocol Title: Can pregabalin reduce the frequency and severity of dry eye symptoms after laser-assisted in situ keratomileusis?

IRB Review History*: None

Objectives:

Specific Aim: Demonstrate the feasibility of preventing DE symptoms after LASIK by peri-operative administration of a gabapentinoid.

Background:

Laser in-situ keratomileusis (LASIK) is a commonly performed surgical procedure used to correct refractive error. While visual outcomes after surgery are excellent, it is well known that a proportion of patients develop persistent dysesthesias after surgery. LASIK involves cutting a corneal flap and ablating the stroma underneath, with long-lasting disruption of corneal innervation.^{3,41} Available data suggest that approximately 20-55% of the 650,000 cases annually report persistent (generally regarded as at least 6 months post-operation) eye symptoms after LASIK surgery. While it was initially believed that these symptoms were caused by ocular surface dryness, and referred to as "dry eye", it is now increasingly understood that corneal nerve damage produced by LASIK may resemble the pathologic neuroplasticity associated with nerve injuries after other forms of persistent post-operative pain.⁴ In susceptible patients, these neuropathological changes, including peripheral sensitization, central sensitization, and altered descending modulation, may underlie certain persistent DE symptoms after LASIK surgery. It is not surprising, therefore, that current treatments, which target the ocular surface, are often not adequate.^{2,3} Persistent DE symptoms after LASIK range in severity, but the deleterious effects on quality-of-life may be significant. Utility studies are used to quantify patient experiences and preferences regarding a disease state, and these have found moderate-to-severe dry eye (DE) equivalent to moderate-to-severe angina or hospital dialysis, while mild DE might equate with severe migraines. These LASIK-induced side effects were deemed important enough by the Food and Drug Administration (FDA) to warrant an investigation on this procedure in 2009.

Our program is focused on the critical steps needed to improve outcomes after LASIK, which will require a better understanding of the epidemiology of this condition (e.g. frequency, characteristics, severity, vulnerable patient groups), understanding mechanisms of susceptibility potentially common to other forms of DE and comorbid conditions⁴ (e.g., peripheral sensitization, central sensitization, comorbid pain conditions, comorbid mental health problems), as well as the study of potential new treatments targeting the pathologic neuroplasticity that occurs and likely underlies persistent symptoms after surgery.

Our long-term goals are to understand the neuro-ophthalmologic pathophysiology induced by LASIK, and improve preventive approaches and therapeutic management of persistent corneal somatosensory system dysfunction caused by LASIK. Our central thesis is that persistent DE symptoms after LASIK can be quantified using a comprehensive assessment protocol that we have developed and symptoms may be prevented by neuromodulators. Specifically, we will test our hypothesis that the use of perioperative pregabalin will decrease the frequency of persistent DE symptoms after LASIK surgery.

Inclusion and Exclusion Criteria*

Study population/recruitment: Subjects will be recruited from Bascom Palmer Eye Institute (BPEI) refractive center and eligible subjects will be informed about an opportunity to participate in the research study.

Inclusion criteria: We will enroll patients between 18 and 65 years of age who are undergoing LASIK (unilateral or bilateral procedure). Females of child-bearing age will need a negative urine or serum β -HCG

test at the screening visit. We will enroll patients whose ocular and systemic medication regimen has been stable for 3 months and we will ask patients to refrain from taking any eye drops (i.e. artificial tears) for at least 2 hours prior to testing.

Exclusion criteria: We will exclude patients who are pregnant or lactating, participating in another study with an investigational drug within one month prior to screening, use gabapentin, pregabalin, anti-convulsants, duloxetine, venlafaxine (SNRI), or tri-cyclic antidepressants, have a history of allergic, anaphylactic reaction, or severe systemic response to pregabalin or gabapentin; use corticosteroids chronically or during the month prior to surgery, or have a history of corneal disease (HSV or VZV keratitis, prior corneal incisions (cataract surgery, RK, LASIK), prior corneal ulcer). We will also exclude patients with systemic co-morbidities that may confound DE such as HIV, sarcoidosis, graft-versus host disease or a collagen vascular disease.

We will exclude the following individuals:

- Adults unable to consent
- Individuals who are not yet adults (infants, children, teenagers)
- Pregnant women
- Prisoners

Exclusion of non-English Speaking Subjects:

For the time being, we will only enroll English speaking subjects. If the prevalence of solely Spanish-speaking subjects dramatically increases, we will consider submitting an IRB approval for a Spanish-translated consent. The Sub-PI and lead coordinator are both fluent in Spanish. The reason for this is due to the following: after confirming with LASIK Eye Center staff, there is only a prevalence rate of 10% of the LASIK surgery patients that do not speak / read the English language. This low percentage is not significant enough to serve as a factor in considering translation of English materials into Spanish. Bascom Palmer staff has confirmed that 90% of their patients lined up for LASIK do in fact speak and read the English language, eliminating any potential bias or discrimination in recruiting subjects.

Number of Subjects:

100 patients are to be recruited at all sites; 60 patients are to be recruited at the Miami site.

Study-Wide Recruitment Methods:

The Naval Medical Center San Diego will also recruit 50 patients under a separate IRB. They will use the same recruitment methodology/inclusion/and exclusion criteria.

The University of Miami will be the coordinating center. Original source documents will be kept at each institution. All data will be entered into a REDCAPs database housed at the University of Miami.

Study Timelines:

- The duration of an individual subject's participation in the study: 6 months
- The duration anticipated to enroll all study subjects: 6 months
- The estimated date for the investigators to complete this study (complete primary analyses): 1 year.

Study Endpoints*

Describe the primary and secondary study endpoints:

Primary: Comparison of dry eye symptom severity (dry eye questionnaire 5 score) at 6 months between the two group.

Secondary: Comparison of all other dry eye metrics and 3 and 6 months. Other questionnaires, OSDI, NPSI, sf-MPQ, NRS, other signs: tear production, evaporation. Analysis of which baseline factors (demographics, treatment, etc.) predict persistent symptoms at 6 months, independent of randomization group.

Describe any primary or secondary **safety endpoints**: Telephone assessment of side effects after the 2 weeks on therapy (placebo versus drug).

Procedures Involved*

Describe and explain the study design.

Summary of study visits:

	V1: Baseline / Randomization (1.5 hours)	V2: 1 day prior to LASIK (Telephone Reminder)	V3: 15 days (telephone visit) ± 1 Day	V4: 3 months (45 minutes) ± 14 Days	V5 : 6 months (45 minutes) ± 14 Days
Informed consent	X				
Questionnaires + Subject Diary	X			X	X
Ocular surface assessment	X			X	X
Cutaneous sensitivity	X				X
Confocal scan	X				X
Blood Draw	X				
Start medication		X			
Con Med / AE Review			X	X	X

Provide a description of all research procedures being performed and when they are performed: All research procedures will take place at Bascom Palmer Eye Institute, Miami. (a) blood will be obtained in the 1st floor clinical laboratory; (b) a waiting area will be utilized for questionnaire completion (3rd floor); (c) one room for ocular surface testing (including cutaneous sensitivity) (3rd floor); (d) confocal microscopy obtained in the imaging area (3rd floor).

Describe:

- Procedures performed to lessen the probability or magnitude of risks: All procedures are standard of care for evaluation of the ocular surface with the exception of cutaneous sensitivity testing which is standard of care in research of somatosensory function.
- All drugs used in the research and the purpose of their use, and their regulatory approval status: Lyrica 150 mg BID and placebo will be used (30 patients in each group). Lyrica has been approved by the FDA for this use (peri-operative treatment to lessen the risk of persistent post-operative pain in other surgeries) but has not been used in conjunction with LASIK surgery.
- All questionnaires used in the study are attached.

DE questionnaires (baseline, 3 months, 6 months): Two validated DE questionnaires, the DEQ5⁵ and the OSDI⁶ will be administered (baseline, 3 months, 1 year). The DEQ5 collects patient responses regarding tearing, dryness, and discomfort independent of visual function, while the OSDI includes visual function and questions related to difficulty with daily activities such as reading, using a computer, nighttime driving, and watching television.^{6,80}

Ocular pain questionnaires (baseline, 3 months, 6 months): Assessment of pain characteristics plays a critical role in research on mechanisms of pain and its treatment.⁶³ **Preliminary data:** We have demonstrated feasibility of using ocular pain questionnaires (short form McGill Pain Questionnaire (sf-MPQ)⁶⁴ and neuropathic pain symptom inventory (NPSI)⁸, in 154 patients with DEQ5 scores ≥ 6 (clinically relevant DE symptoms).²² 82% of subjects were found to endorse at least 1 sensory or 1 affective descriptor for their eye pain on the SF-MPQ. Subjects most frequently described their ocular pain as "tiring-exhausting" (56%),

followed by "aching" (56%), and "hot burning" (53%). Regarding the NPSI, the most common neuropathic-like symptoms were allodynia and hyperalgesia provoked by light, wind, or hot/cold, spontaneous burning pain, and pressure pain. Total scores on the SF-MPQ and the NPSI were highly correlated with each other (Pearson $r = 0.72$; Spearman $\rho = 0.71$, $p < 0.001$), and both were highly correlated with NRS ratings of eye pain ($r = 0.61$ (SF-MPQ vs. NRS); $r = 0.71$ (NPSI vs. NRS)). Testing:

Ocular pain: We will administer three questionnaires, each targeting different aspects of pain: NRS of ocular pain intensity (range 0-10) over various recall periods; sf-MPQ⁶⁴, consisting of 15 words including sensory and affective descriptors of pain (range 0-45); NPSI⁸, specifically developed to evaluate for different symptoms of neuropathic pain (range 0-100). In our modified version of NPSI we replaced standard questions 8, 9, and 10 of the original items regarding allodynia and hyperalgesia (pain caused by (1) brushing, (2) pressure, or (3) cold *on the skin*), with items specific to ocular allodynia and hyperalgesia (*eye pain* caused or worsened by (1) light, (2) wind, and (3) heat or cold).

OCULAR SURFACE TESTING

(*) **Tear osmolarity** (TearLAB, San Diego, CA) testing will be performed once in each eye prior to instillation of eye drops. The osmolarity hand-piece will be held over the outer 1/3 of the inferior conjunctivae to sample the inferior tear meniscus. Patients will be asked to look up and nasally during the testing.

(*) **Inflammadry testing (RPS, Tampa, FL):** A tear sample will be collected by exposing the lower palpebral conjunctiva and gently dabbing the fleece of the sample collector temporally to nasally approximately 6-8 times, allowing the patient to blink between dabs to ensure saturation. The sampling fleece will glisten or turn pink when an adequate sample is collected and then will be snapped into the test cassette prior to immersion of the absorbent tip into the buffering solution for approximately 20 seconds or until a purple wave appears in the cassette window. The cap will then be replaced over the absorbent tip and the applicator will be laid flat for 10 minutes before interpretation of test results.

(iv) **Tear film break up time (TBUT):** The examiner will gently retract the upper lid and 5 μ l of preservative free fluorescein will be placed on the superior bulbar conjunctivae. The upper lid will be released and the subject will be allowed to blink normally for 15 seconds. The patient's head will be positioned in the headrest of the slit-lamp instrument, making sure the patient is comfortably supported with their forehead in full contact with the headrest band. The patient will be instructed to blink three times naturally, then stare and NOT BLINK. The investigator will monitor the integrity of the tear film and, using a stopwatch, measure the time from the last blink until one or more black (dry) spots appear in the precorneal tear film. After the 1st measurement, the patient will be instructed to blink naturally 3 additional times and a 2nd measurement is taken. The procedure will then be repeated a 3rd time. After a 60-second rest period, the entire procedure will be repeated for the left eye.

(*) **Conjunctival and corneal staining** will be assessed using the NEI standard scoring scale assessing 5 areas of the cornea and 6 areas of the conjunctivae.¹⁰⁰ This will be done directly after TBUT testing. A grade (0-3) will be assigned to each section of the cornea and a total score (0-15) will be generated by summing the 5 section scores. Regarding the conjunctiva, 10 μ l of lissamine green will then be placed in the inferior fornix of both eyes. After 3 minutes, the examiner will divide the conjunctiva into a superior paralimbal area, an inferior paralimbal area and a peripheral area with a grading scale of 0-3 for each area (maximal score of 9) for both the nasal and temporal conjunctiva.

(*) **Eyelid assessment:** The presence of lower eyelid laxity will be determined by the snap back test (0=laxity within normal limits, 1=a delay of two to five seconds for the lower lid to return to its native state, 2=persistent separation necessitating a blink to return to the normal state). Upper eyelid laxity will be determined by the lid distraction test (0=laxity within normal limits, 1= 7-10 mm of distraction, 2 =

greater than 10 mm of distraction). Conjunctivochalasis will be graded as absent or present in each area of the lower eyelid (temporal, central, nasal) based on the obliteration of the tear film by conjunctivae in the region of interest. The degree of eyelid vascularity will be scored on a scale of 0 to 3 (0=none; 1=mild; 2=moderate; 3=severe) as will the degree of inferior eyelid meibomian orifice plugging (0=none; 1=less than 1/3 lid involvement; 2=between 1/3 and 2/3 lid involvement; 3 greater than 2/3 lid involvement). The presence of fibrosis, papillary, or follicular conjunctival changes will be determined as absent or present.

(*) Schirmer strips will be placed in the outer 1/3 of the lower conjunctivae and the length of wetting after 5 minutes will be recorded in each eye. No anesthesia will be used prior to Schirmer strip placement.

(*) Meibum quality will be rated on a scale of 0 to 4 (0=clear; 1=cloudy; 2=granular; 3=toothpaste; 4=no meibum extracted).¹⁰³

(*) ConfoScan 4 (Nidek Technologies Srl, Padova, Italy): Examination will be carried out using the 40X lens of the Confoscan 4. Before the examination, a drop of topical anesthetic 0.5% proparacaine hydrochloride (Alcon, USA) will be used to anesthetize both eyes. A drop of Genteal gel (0.3% Hypromellose, Alcon Laboratories, Inc., USA) will be applied onto the lens tip. The patient will be seated in front of the microscope with chin rest and forehead support in place and asked to fixate the examined eye to the light inside the lens. The joy stick will move the lens toward the eye until the gel contacts the cornea. The device alerts the operator when the stroma appears on the monitor, after that, a button is pressed to initiate recording. The device automatically completes the alignment and acquires several corneal scans at a speed of 25 frames per second, obtaining 350 images per scan, every 3 μm for the anterior mode scan. Each image represented a coronal section of 460 X 345 μm (158,700 μm^2) with a minimum axial step of 1 μm , magnification of X500, and lateral resolution of 0.6 $\mu\text{m}/\text{pixel}$. Two good quality images of the sub-basal nerve plexus will be selected and run through the Corneal Nerve Analysis tool (Nidek Technologies Srl, Padova, Italy), a new nerve analysis software program. The criteria of selection will be (1) best focused image with (2) good contrast and (3) the complete image in the same layer. Automated analysis performed by this software tool will be augmented with manual refinement to improve the analysis accuracy. Manual refinement will be performed on a step-by-step basis by selecting or tracing required parameters, which remain undetected by automatic analysis. A variable amount of refinement is needed depending on the quality of the image. The 9 parameters captured include: 1- Nerve fibers length (NFL) was defined as the total length of the nerve fibers (in micrometers) per frame ($\mu\text{m}/\text{frame}$). 2- Nerve fibers length density (NFLD) was defined as the total length of the nerve fibers (in micrometers) in this layer divided by the area of the frame ($\mu\text{m}/\text{mm}^2$). 3- Number of trunks (defined as the total number of main nerves in one image). 4- Number of branches (defined as the total number of nerve branches in one image). 5- Number of fibers (defined as the total number of nerve fibers, including nerve trunks and branches, in one image). 6- Number of bifurcations (defined as the total number of nerve bifurcations in one image). 7- Number of beadings (defined as the total number of well-defined hyper-reflective points in all identified main nerves (trunks) in one image). 8- Beading density (defined as the total number of nerve beadings in one image divided by the total length of nerve trunks in millimeter (beadings/mm)). 9- NIDEK Nerve fibers tortuosity (a unit-less measure that represents the degree of curvature of nerve fibers). The average time for manual optimization and analysis of each image is 3.5 (+/- 0.5) minutes.

Cutaneous QST: Dr. Felix has 20 years of experience utilizing QST methods for assessing somatosensory function in a variety of patient groups and healthy, control subjects. Preliminary data: One previous group utilized QST in DE and found that subjects with DE had lower heat pain thresholds and tolerance levels (higher pain sensitivity) on the forearm.⁷² These data suggest that DE subjects as a group have increased sensitivity to thermal stimuli in an area remote from the eye. In our protocol, we test a site (forehead) to look for receptive field expansion (secondary hyperalgesia), as forehead primary nerves

converge into the trigeminal ganglion with corneal nerves, as well as a remote site (forearm^{51, 73, 74}) where abnormalities of sensory function suggest the potential for central (thalamus and cortex) system involvement. We also apply testing protocols thought to be more specific for central sensitization (temporal summation (TS)) and descending inhibition of pain (conditions pain modulation (CPM)). Specifically, persons with certain chronic pain conditions have been shown to express greater summation of pain due to repetitive presentations of a noxious stimulus^{75, 76} and muted descending pain modulation⁷⁷, compared to those without chronic pain. **Testing: Mechanical pain thresholds (MPT):** A standard set of pin prick stimulators (UNC-Chapel Hill, Biomedical Engineering Core) will be used to measure mechanical pain thresholds. This specialized set consists of 7 graded monofilaments, with a range of pressures between 8 and 512mN, with smooth tip geometry that is consistent across all 7 filaments and does not penetrate skin. Each subject will be instructed to respond to each test as to whether or not the stimulus felt painful to them. On each trial, the pin prick stimulator is applied perpendicular to the test site on the skin and held in place for ~1 sec. Two stimulus series will be performed at each site according to the method of limits.⁷⁸ MPT will be defined as the arithmetic mean of the values obtained on ascending and descending stimulus series. **Temporal summation:** Temporal summation will be measured only at the forearm test site. Using the 256mN pin prick stimulator, we will first present a single stimulus on the forearm and ask the subject to rate the intensity and unpleasantness of the pain generated. Then we will present a train of 10 stimuli (one second "on", one second "off") and ask the subject to rate the peak pain intensity and unpleasantness. Measures of TS will be obtained by subtracting the rating of the first stimulus from the peak pain. **Conditioned pain modulation:** After the baseline temporal summation protocol (described above) is performed on the right forearm, a noxious "conditioning" stimulus is presented to the left hand (immersion in a cold water bath for 60 sec), then a second set of measures of pin prick temporal summation is performed. The magnitude of conditioned pain modulation is calculated by subtracting ratings of pain during baseline temporal summation from ratings of pain during temporal summation procedures performed after the conditioning stimulus. Lower ratings for post- compared to pre-conditioning ratings indicate greater descending modulation of pain. No reduction, nor an increase, in pain ratings suggests dysfunction within the descending tracks of the system.⁷⁹

Assessed co-morbidities: Many factors, besides gabapentoid use, can affect DE symptoms including medication use (prescription and over the counter) and co-morbidities (depression). As such, we will rigorously collect information on variables of interest and in secondary multivariable analyses, evaluate the impact of these co-morbidities on DE symptoms and ocular pain after LASIK. Co-morbidities to be collected include (a) ocular and systemic medications; (b) ocular and systemic co-morbidities (diabetes, hypertension); (c) non-ocular pain via a pain history questionnaire; (d) depression and anxiety via the Patient Health Questionnaire (PHQ-9) and the SCL-90R; and (e) QoL via the SF-12 health survey (physical and mental components).

Data and Specimen Banking*

(1) **Blood samples** will be stored and genomic DNA (gDNA) isolated and genotyped at Hussman Institute of Human Genomics (HIHG), Biorepository and Genotyping Cores: 1501 NW 10th Avenue BRB 450. Miami, FL 33136. All blood samples will be stored in a de-identified fashion with a unique identifier. We plan on storing the blood so that we can later analyze which genetic polymorphisms associated with persistent post op symptoms.

(2) **Tear samples** will be stored in a -80 °C freezer in a de-identified fashion in the McKnight Vision Research Center, next door to the Bascom Palmer Eye Institute located at 1638 NW 19th Ave, Floor 7. Miami, FL 33136. They will later be used to quantify proteins and lipids (e.g. inflammatory mediators) that predict persistent post op pain.

Data Management*

Organizational Structure: Study activities will be centered at BPEI refractive clinic located on the 3rd floor and administrative activities will take place in room 275 on the 2nd floor of the same building. Dr. Galor, the PI, will have responsibility over all aspects of the study. Dr. Galor will work closely with Dr. Levitt with extensive experience with the design and execution of Phase 1 - 4 clinical trials in academia and industry and William Feuer, a biostatistician with decades of experience in the design and conduct of ophthalmic clinical trials.

Randomization: Eligible individuals will be randomly assigned, in a ratio as close as possible to 1:1, to either the control or the treatment group according to the randomization schedule prepared by the biostatistician (Mr. Feuer). A variable ($n=2$ or $n=4$) blocked randomization list for treatment assignments will be constructed to ensure that treatment assignments are balanced after, at most 4 patients. Once prepared, a copy of the randomization schedule will be given to the BPEI pharmacist who will be in charge of dispensing the study capsules to each participant according to the group to which the participant was assigned. The pharmacist will be in close communication with the biostatistician who will deal with any issues regarding the randomization schedule.

Statistical analysis: Statistical analyses will be performed using SPSS 21.0. Before the implementation of any statistical tests, we will use descriptive statistics to assess the distributional properties of the different variables and their interrelationships, as well as to determine missing data and to detect outliers. Transformations will be used for variables with skewed distributions before their inclusion in analyses that require normality or approximate normality. If normality cannot be achieved, then nonparametric techniques will be used. The amount of missing data will be minimized through rigorous data quality control procedures implemented from the start of the study. But, as is the usual case in clinical studies, missing data may occur. Whenever appropriate, missing data will be imputed using mean-based or regression-based imputation procedures. All analyses will be performed on an intent-to-treat basis, i.e., for purposes of statistical analyses, all participants will be considered in the group to which they were originally randomized. All statistical tests will be two-sided tests, conducted at a nominal 5% level of significance. Study participants will be randomized to two groups, "control" and treatment, and outcome variables as well as potential confounders will be ascertained at baseline (0 months) and at 3 and 6 months. The principal statistical analysis for this study will be a frequency comparison of DE symptoms ($DEQ5 \geq 6$; or mild to severe) between the two groups (Fisher exact or Chi square methodology) at 6 months. Secondary analyses will include the effect of medication on secondary end-points including measures of tear and somatosensory function (trigeminal and distal sites). Multi-variable analyses will be conducted to consider the contribution of demographics, baseline examination findings, and LASIK treatment parameters. We will use this study to assemble the team, demonstrate the protocol is functioning and establish if there is any trend, all of which are needed in order to submit a competitive U-type NIH proposal for a larger, multi-centered RCT that will replicate and extend our program.

Power considerations: Published data suggest that upwards of 55% of patients will experience persistent DE symptoms at 6 months. A RCT with pregabalin dosing before and for 2 weeks after surgery, similar to our proposed protocol, demonstrated a 100% response rate in patients undergoing total knee arthroplasty (TKA).³⁵ Using the Fisher's exact test to compare our proposed groups (30 patients in each group), a 0% frequency of PPP at 6 mos. (as in the TKA paper)³⁵ in the treatment group and a 55% frequency of PPP in the placebo group would yield a highly significant p value of <0.0001 . Assuming a treatment response of 44% (24% frequency of PPP at 6 mos.) in the treatment group and a 55% frequency of PPP in the placebo group, we would still have the power to show a significant difference between groups ($P=0.042$). *The importance of our first-of-a-kind feasibility study of perioperative pregabalin cannot be overstated.* From this groundbreaking study we should have sufficient epidemiologic and symptom-response data to design and conduct a large well-controlled well-powered multicenter RCT of pregabalin for the prevention of persistent DE after LASIK. The table below gives necessary sample sizes for a range of treatment efficacies, 75% to 95%, at both 80% and 90% power assuming analysis with the Fisher exact test

and an alpha error of 0.05. If the treatment is 75% effective a sample of 30 per group would provide 80% power.

	Placebo control group incidence 55%			
	Effectiveness of treatment			
	75%	85%	90%	95%
Expected Incidence in actively treated group	14%	8%	6%	3%
Sample size per group for 80% power	25	18	17	15
Sample size per group for 90% power	31	22	20	18

Randomization: Eligible individuals will be randomly assigned, in a ratio as close as possible to 1:1, to either the control or the treatment group according to the randomization schedule prepared by the biostatistician (Mr. Feuer). A variable (n=2 or n=4) blocked randomization list for treatment assignments will be constructed to ensure that treatment assignments are balanced after, at most 4 patients. Once prepared, a copy of the randomization schedule will be given to the BPEI pharmacist who will be in charge of dispensing the study capsules to each participant according to the group to which the participant was assigned. The pharmacist will be in close communication with the biostatistician who will deal with any issues regarding the randomization schedule.

Data management: A log will be created to track all data collection activities. The log will specify data are to be collected for each participant as well as the expected and actual dates of collection. Reports of completed assessments will be generated to plan requirements for participant follow-up. Under the study Biostatistician's supervision, staff will be trained in necessary activities related to data collection, management and quality control. All source data will be stored in a secured location. In addition, we will work with a data manager to create a data collection sheet in REDCAP. All data will be inputted into REDCAP. All of the research staff will have updated training, authorization of access, all electronic documents (ie REDCAPS) will be password protected and only those authorized will be able to enter and see the data. In addition, only the source documents will have the patient identifier. All data in REDCAPS will be stored with a unique identifier and not with patient identifying information.

Describe any procedures that will be used for quality control of collected data: The study coordinator will put all the data in REDCAPS which will be built with quality control measures (ie not being able to put in a value that is not possible). In addition, other study members will perform periodic quality control checks on 10% of the data to ensure good quality. We will also evaluate data quality on a monthly basis by examining descriptives of all the data collected.

- What information will be included in that data or associated with the specimens? Only a unique identifier will be stored with the specimens.
- Where and how data or specimens will be stored? Source data will be stored in locked cabinet of study coordinator. Electronic, de-identified data will be stored on REDCAPS
- How long the data or specimens will be stored? Data for 20 years. Specimens until they are used.
- Who will have access to the data or specimens? Only those listed on the IRB protocol including coinvestigators, statistician, study coordinator, and PI.
- Who is responsible for receipt or transmission of the data or specimens? Study coordinator and PI will be responsible.
- How data and specimens will be transported? Data electronically. All specimens will be housed locally at UM.

Provisions to Monitor the Data to Ensure the Safety of Subjects*

Risks to Human Subjects Human Subjects Involvement, Characteristics, and Design

Proposed involvement of human subjects: Patients will be prospectively recruited from Bascom Palmer Eye Institute (BPEI)).

Description and justification of the characteristics of the subject population: A total of 50 patients will be recruited into the proposed study based on the performed power calculation. As we plan to recruit patients from Miami-Dade county hospitals, we anticipate that the racial/ethnic characteristics of the subject population will reflect the demographics of Miami-Dade County.

Description and justification the sampling: As this study poses minimal risk to the patient, further testing will occur on the same day as signing of the informed consent. The research procedures include questionnaires and ocular surface evaluation (3 times), tear sample collection and analysis (3 times), and genetic analysis (one time).

Recruitment Methods: All eligible patients who plan on undergoing LASIK seen at the Bascom Palmer Eye Clinic will be offered recruitment into the study. The study coordinators will explain the study goals, the required evaluations, the necessary follow up, and the potential risks. Subjects will be asked for their voluntary participation and if they agree, adequate time will be given to read and review the informed consent. An IRB- approved study flyer will be placed in an 8.5 x 11 flyer holder within several exam rooms in the Lasik Vision Center as well as the waiting room.

Sources of Materials

Research material: Information obtained in the course of the study will include: demographic information, past ocular and medical history, and use of medications. Several questionnaires will be administered which will collect information on presence of DE symptoms, ocular pain, and co-morbidities (depression, PTSD). Testing will include cutaneous sensitivity measurements; Patient tears and blood will be collected for later analysis. Each patient will be assigned a unique identifier and samples will be stored and analyzed with the unique identifier information only. The medical data obtained from participants will include demographic information, medical and surgical history, and medication information. Data will be collected on paper and converted to an electronic form (REDCAPS). The document will not include individually identifiable private information and will identify patients using their unique identifier. A separate document will link each unique identifier to a patient. All electronic and paper data will be stored in the locked offices of the study coordinator. Only the principal investigators and study coordinators will have access to individually identifiable private information.

Potential Risks

During the study, they will be asked to fill out a questionnaire that asks questions about depression, anxiety, and pain. If these questions become too distressful for the subject to complete, and they do not wish to take part in this portion of the study, they will not be able to participate in this study.

All subjects will undergo DE testing including osmolarity measurement, slit lamp examination, Schirmer's testing, MMP9 measurement using *Inflammadry*, and tear collection. These tests pose no significant risks to the patient. All patients will undergo cutaneous sensitivity measurements. There is no risk of damage to the eye or skin with sensitivity testing. All patients will also be asked to provide a blood sample for genetic

analysis. The risks associated with the blood draw are minimal and include pain, hematoma formation, and in rare cases, infection. As in all studies, there is a risk that non-authorized individuals will gain access to patient information. We will mitigate this risk by keeping all sensitive information behind locked doors and password protected, with only authorized users having access. All study related procedures are being done for research purposes only. All procedures are the best available to study the research questions.

Potential Drug Side Effects:

The most common side effects of pregabalin include:

- Tiredness
- Dizziness
- Headache
- Dry mouth
- Nausea or vomiting
- Constipation
- Gas or bloating
- "High" or elevated mood
- Swelling of the arms, hands, feet, ankles, or lower legs
- Back pain

Interactions:

Drug interactions may change how your medications work or increase your risk for serious side effects. This document does not contain all possible drug interactions. Keep a list of all the products you use (including prescription/nonprescription drugs and herbal products) and share it with your doctor and pharmacist. Do not start, stop, or change the dosage of any medicines without your doctor's approval. A small number of people who take anticonvulsants for any condition (such as seizure, bipolar disorder, pain) may experience depression, suicidal thoughts/attempts, or other mental/mood problems. Tell your doctor right away if you or your family/caregiver notice any unusual/sudden changes in your mood, thoughts, or behavior including signs of depression, suicidal thoughts/attempts, thoughts about harming yourself.

A very serious allergic reaction to this drug is rare. However, get medical help right away if you notice any symptoms of a serious allergic reaction, including: rash, itching/swelling (especially of the face/tongue/throat), severe dizziness, trouble breathing.

Adequacy of Protection against Risks

The study coordinator will explain the study goals, the required testing, and the potential risks. Only subjects with the mental capacity to understand the study and the informed consent process will be recruited. Subjects will be asked for their voluntary participation and if they agree, adequate time will be given to read and review the informed consent. The principal investigators will be available to answer any further questions. The study coordinator will document that the consent was properly obtained.

Protection against Risk: Patients will be assured that refusal to participate in the study will in no way compromise the care they receive. With regards to data protection, all data will be de-identified to protect patient privacy.

Potential Benefit of the Proposed Research to the Subject and Others: This project has the potential to directly benefit the subject as the use of pregabalin may decrease the frequency and severity of dry eye symptoms after LASIK.

Importance of the Knowledge to be gained: Important knowledge will be gained from the study as its findings will improve our understanding of persistent dry eye symptoms after LASIK and their potential reduction.

Data and Safety Monitoring. The research team will meet on a weekly basis to review study criteria, recruitment, safety, and data integrity issues. The principal investigators will have the overall responsibility of ensuring patient safety and accuracy of data but will have a full time study coordinator to help with these endeavors. The study coordinator will review all study documents prior to the patient leaving to minimize the risk of missing data. The database will be reviewed by the PIs on a weekly basis to ensure that all information is collected and stored appropriately. The final data regarding efficacy will only be available after all subjects complete the study as the investigator and study coordinator will be masked to the drug randomization. Specifically, after the two weeks of therapy, a phone survey will be conducted to assess side effects in all patients. In person side effect checks will also be done at the 3 and 6 month visit although no active drug (or placebo) will be used beyond the initial 2 week period. There will be two levels of safety monitoring during the course of the clinical trial that are commensurate with risk based on the nature, size and complexity of this trial. Our protocol utilizes pregabalin for a new indication consistent with approved indications to treat persistent neuropathic pain at the same dose and route of administration. Therefore, our Safety Monitoring Plan will include: 1) ongoing timely evaluations by the clinical trial team, and 2) institutional oversight by the University of Miami Institutional Review Board (IRB). All AEs will be recorded in participants' medical records. AEs will be graded and attribution assigned. The study technicians, coordinators and PI will meet weekly to review the progress of the study, including all AEs. Expected protocol-related AEs (e.g. dizziness and gastrointestinal upset) will be reported to the IRB during annual ongoing reviews. Unexpected and severe adverse events (SAE) include hospitalization, life-threatening condition, permanent or substantial disability, test-drug overdose, falls, any important medical event, and death will be reported to the IRB in an expedited fashion. The PI will ensure accurate documentation and investigation and follow-up of all possible study-related adverse events. The cumulative incidence of adverse events (AEs) will be recorded over the 6-month period.

Withdrawal of Subjects*

Subjects may withdraw from the study at any time point. Data already collected will be included for the secondary endpoint analysis, if permitted by the patient.

Vulnerable Populations: N/A

Multi-Site Research:

If this is a multi-site study where you are the lead investigator, describe the processes to ensure communication among sites, such as:

Once Miami IRB approves the protocol/ICF, we will share all documentation with the San Diego site. They will be responsible for obtaining their own IRB approval. We will have monthly calls with San Diego to discuss study related issues and meet in person twice a year at ophthalmology meetings.

The same safety checks that will be implemented in Miami will also be carried out by the San Diego site.

The subject's identity and records will be kept as confidential as possible as required by law and will not be made publicly available. Except as required by law, subjects will not be identified on any study form by name, Social Security number, address, telephone number, or any other direct

personal identifier. Instead, they will be assigned a subject enrollment ID. The study doctor will keep a list that matches participant identification numbers to participant names and will only share the following information with the San Diego site: age, gender, race, current medications, and medical history. It is possible that this other information could be used to identify the subject even though their names do not appear.

Medical information collected during this study and the results of any test or procedure that may affect the medical care of the subject may be included in their medical record. The information included in their medical record will be available to health care providers and authorized persons including the subject's insurance company.

During their participation in this study, they will have access to their medical records and any study information that is part of that record.

The results of this research may be presented at scientific or medical meetings or published in scientific journals. In this case, the subject's identity will not be made known.

Community-Based Participatory Research

N/A

Sharing of Results with Subjects*

Once the data is analyzed and the paper written, we will mail each subject a letter explaining the study findings and thanking them for their participation in the study.

Setting

All subjects will be identified and recruited within refractive surgery screening clinics at Bascom Palmer Eye Institute.:

Resources Available

All study personnel will have all their CITI courses completed. The study coordinator will work with the IRB to ensure compliance with all regulatory responsibilities.

Approximately 900 refractive procedures are performed at BPEI per year, and approximately 80% of those are LASIK procedures. Most subjects who plan to undergo LASIK would qualify for enrollment in this study. 50% of my time at the University of Miami will be devoted to performing this clinical trial.

Facilities to be used: BPEI has all facilities required to perform LASIK (Sonia Yoo, William Culbertson), randomize patients to placebo/drug (Bill Feuer), prepare and dispense the medications to the patients (Serafin Gonzalez), perform an ocular surface examination (Carmen Perez Blanco; backup: Ailen Gutierrez), and cutaneous sensitivity testing (Elizabeth Felix; backup: Ailen Gutierrez).

Bascom Palmer Eye Institute has a Clinical Research Unit with resources and expertise in carrying out research, including anticipating or unanticipated medical or psychological issues that may arise.

All personnel will be CITI certified, all will undergo training by Dr. Galor prior to initiation of the study, and weekly meetings will be held to ensure adherence to the protocol and research procedures.

Prior Approvals

None

Recruitment Methods

Patients will be asked to participate if they are deemed a candidate for LASIK by Dr. Carmen Perez Blanco and if they plan to have their LASIK done at BPEI.

Patients coming for a refractive surgery evaluation at BPEI.

Describe the methods that will be used to identify potential subjects. Dr. Perez-Blanco will screen the patients for their appropriateness for LASIK (as part of clinical care) and also for potential enrollment in the study.

Describe the amount and timing of any payments to subjects. Subjects will be given \$50 for participating in the first visit, \$25 for the 3 month visit and \$50 on the last visit (total \$125).

Local Number of Subjects

60

Confidentiality

- All source documents will be stored in the office of the study coordinator in a locked cabinet. In addition, all electronic information will be stored on REDCAP in a de-identified fashion.
- Data and specimens will be stored locally for 10 years.
- Only approved study personnel (PI, study-coordinator, data manager, and statistician) will have access to the data and specimens locally.

Provisions to Protect the Privacy Interests of Subjects

The subject's authorization for use of their personal health information does not expire. This information may be maintained in a research repository (database) and may be used as described in this document for any and all study/research-related purposes. Results of all tests and procedures done solely for this research study and not as part of their regular care will be included as part of their medical records. The Human Subjects Research Office Institutional Review Board (UM IRB) is a committee whose job it is to protect the safety and privacy of research participants and results of all tests and procedures done solely for this research study that are not part of their regular care, will be included as part of their medical records.

PRIVACY AND CONFIDENTIALITY

Subjects' identity and records will be kept as confidential as possible as required by law and will not be made publicly available. Except as required by law, they will not be identified on any study form by name, Social Security number, address, telephone number, or any other direct personal identifier. Instead, they will be assigned a participant identification number. The study doctor will keep a list that matches participant identification numbers to participant names. However, the study forms will contain other information about the subject, such as age, sex, and medical history. It is possible that this other information could be used to identify them even though their name does not appear.

Medical information collected during this study and the results of any test or procedure that may affect their medical care may be included in their medical record. The information included in their medical record will be available to health care providers and authorized persons including their insurance company.

The results of this research may be presented at scientific or medical meetings or published in scientific journals. In this case, their identity will not be made known.

Other groups may need to look at their medical records and study forms to make sure that the information is correct and to evaluate the conduct of this research study. These include the following:

- University of Miami's Human Subjects Research Office that reviewed this study
- Regulatory agencies in the United States, such as the Food and Drug Administration, Department of Health and Human Services and the Office for Human Research Protections

- Regulatory agencies from other countries where this research study is also being conducted

Compensation for Research-Related Injury

Subjects will be given \$50 for participating in the first visit, \$25 for the 3 month visit and \$50 on the last visit (total \$125).

Economic Burden to Subjects

Taking time away from work to complete 3 study visits.

Consent Process

The consent process will take place at BPEI refractive evaluation clinic. After the screening visit for refractive surgery, if the patient is interested, they may be consented that same day or on the day that they come for their baseline ocular surface examination. The study coordinator will explain all parts of the consent process and will document the process in addition to the consent itself. The subject will have adequate time to read the consent and have all questions answered. We will abide by the SOP: Informed Consent Process for Research (HRP-090).

Subjects who are not yet adults (infants, children, teenagers): N/A

Cognitively Impaired Adults: N/A

Adults Unable to Consent: N/A

Process to Document Consent in Writing

We will follow the SOP: Written Documentation of Consent (HRP-091).

Drugs or Devices

Study drug will be accrued, stored, and compounded at Research Pharmacy for this study ONLY. Controlled substances will be stored in a designated locked cabinet. Storage temperature will be monitored continuously for any possible excursions. Study drugs for other studies will NOT be used for this study and vice versa. Study drug preparation and dispensing will be done by solely by unblinded pharmacists at the Research Pharmacy with technical assistance from pharmacy technicians.